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Copper-catalyzed intramolecular direct amination of sp^2 C–H bonds for the synthesis of *N*-aryl acridones†

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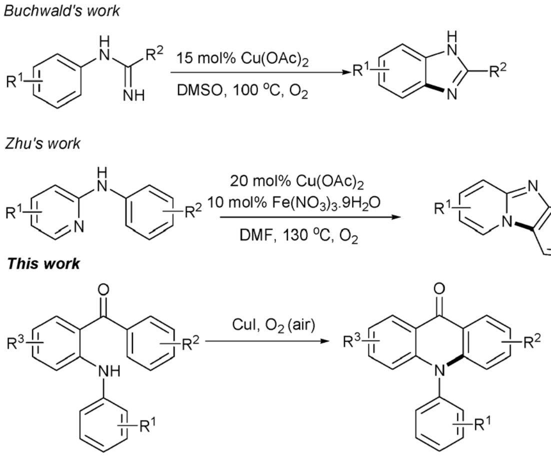
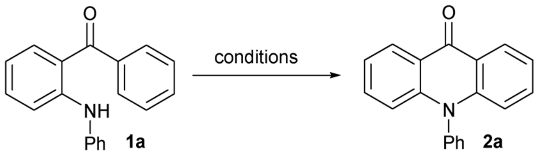
A copper-catalyzed approach for the synthesis of *N*-aryl acridones *via* sp^2 C–H bond amination using air as oxidant under neutral conditions is disclosed. This reaction not only provides a complementary method for synthesizing medicinally important acridones, but also offers a new strategy for sp^2 C–H bond amination.

Transition-metal-catalyzed C–N bond formation is of great importance due to the ubiquity of amino groups in pharmaceuticals, agrochemicals, dyes, and bioactive compounds.[1] Compared with the traditional transition-metal-catalyzed strategies to construct C–N bonds,[2] direct amination of C–H bonds has many incomparable advantages, including atom- and step-efficiency and environmental benignity of the transformation.[3] The reported methods for direct amination of C–H bonds are commonly catalyzed by Pd[4] or Cu[5] catalysts. Terminal oxidants, such as hypervalent iodine(III),[4h,5c] copper(II),[4g] silver(I),[4e,j] and fluorine(I),[4d,i] are indispensable for these methods generally. Among these oxidant candidates, oxygen is obviously considered as an ideal choice due to its inexhaustible, inexpensive, and environmentally benign features.[6] There are a limited number of methods employing cheaper copper salts along with dioxygen as the terminal oxidant in direct intramolecular C–H amination. In 2008, Brasche and Buchwald[5a] reported a copper-catalyzed intramolecular C–H functionalization for the synthesis of benzimidazoles (Scheme 1). Later, Zhu *et al.*[5b] reported a copper(II)/iron(III) co-catalyzed intramolecular amination. In addition, these intramolecular C–H amination methods mostly delivered five-membered ring products. Yet, the homologous intramolecular amination remains a research topic of great value. Moreover, acridones were prepared by the acid-induced ring closure of *N*-phenyl anthranilic acids, nucleophilic substitution of



Scheme 1 Intramolecular C–H amination using the copper–O$_2$ catalytic system.

Table 1 Screening of reaction conditions[a]



Entry	Cat. (mol%)	Solvent	Yield[b] (%)
1[c]	CuI (20)	DMSO	75
2	**CuI (20)**	**DMSO**	**78**
3[d]	CuI (20)	DMSO	14
4	CuI (20)	PhCl/DMSO	77
5	CuI (20)	DMA	62
6	CuI (20)	DMF	37
7	CuI (20)	NMP	62
8	CuI (20)	PhCl	5
9	CuI (20)	Dioxane	Trace
10	CuI (20)	Anisole	Trace
11	CuI (20)	PivOH	Trace
12[e]	CuI (20)	DMSO	0
13	None	DMSO	Trace
14[f]	CuI (20)	DMSO	67
15	CuI (5)	DMSO	Trace
16	CuI (10)	DMSO	42
17	Cu(OAc)$_2$ (20)	DMSO	42
18	CuBr (20)	DMSO	64
19	CuCl (20)	DMSO	54
20	CuBr$_2$ (20)	DMSO	9
21	CuCl$_2$ (20)	DMSO	15
22	Pd(OAc)$_2$ (20)	DMSO	Trace

[a] Reaction conditions: **1a** (0.3 mmol), catalyst, and solvent (1.6 mL) were stirred at 120 °C under air (1 atm) for 48 h. [b] Isolated yield. [c] The reaction was carried out at 140 °C. [d] The reaction was carried out at 100 °C. [e] The reaction was carried out under N$_2$. [f] The reaction was carried out under O$_2$.

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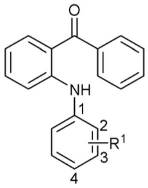
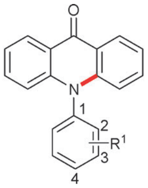
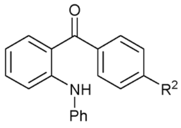
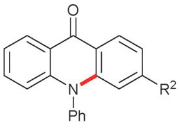
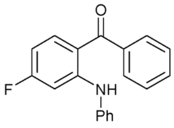
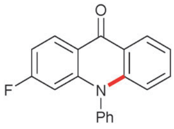
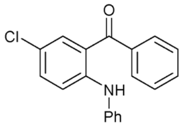
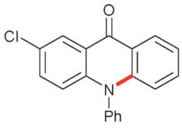
electron-withdrawing groups substituted arenes or the coupling of arynes and benzoates or benzamides traditionally.[7] However, inaccessible substrates and an excess amount of acidic catalysts or reagents are generally required. Herein, we disclose a copper-catalyzed intramolecular direct amination of sp^2 C–H bonds for the synthesis of *N*-aryl acridones using air as oxidant under neutral conditions.

Our study was initiated using phenyl-(2-phenylaminophenyl)-methanone **1a** as the substrate to determine the optimized conditions (Table 1). Substrate **1a** could be smoothly converted to the cyclized product *N*-phenyl acridone **2a** in 75% yield upon the treatment with CuI (20 mol%) and air (1 atm) in DMSO at 140 °C (entry 1). An acceptable yield was obtained at 120 °C (78%, entry 2), but a significantly decreased yield was observed at a lower temperature (entry 3). Except for the mixed solvent DMSO–PhCl (entry 4), other solvent systems failed to provide more favorable outcomes (entries 5–11). The concurrence of CuI and air is crucial for this C–H amination (entries 12 and 13). A comparable yield was observed when the reaction was carried out under O_2 (entry 14). Other copper catalysts, such as CuBr, CuCl, $CuBr_2$, and $Cu(OAc)_2$, led to a decreased yield of products (entries 17–21). Moreover, $Pd(OAc)_2$ could not catalyze the transformation efficiently (entry 22).

Table 2 The direct amination of sp^2 C–H bonds[a]

Entry	Substrate			Product		Yield[b] (%)
		R^1				
1		H	**1a**		**2a**	78
2		2-Me	**1b**		**2b**	73
3		3-Me	**1c**		**2c**	53
4		4-Me	**1d**		**2d**	93
5		4-Ph	**1e**		**2e**	73
6		4-I	**1f**		**2f**	80
7		4-Br	**1g**		**2g**	81
8		4-Cl	**1h**		**2h**	85
9		4-F	**1i**		**2i**	71
10		4-COOEt	**1j**		**2j**	58
11		4-CN	**1k**		**2k**	30
12		4-CF_3	**1l**		**2l**	42
		R^2				
13		Me	**1m**		**2m**	67
14		^{t}Bu	**1n**		**2n**	70
15		OMe	**1o**		**2o**	30
16		OCF_3	**1p**		**2p**	46
17		Cl	**1q**		**2q**	76
18		F	**1r**		**2r**	33
19			**1s**		**2r**	83
20			**1t**		**2s**	85

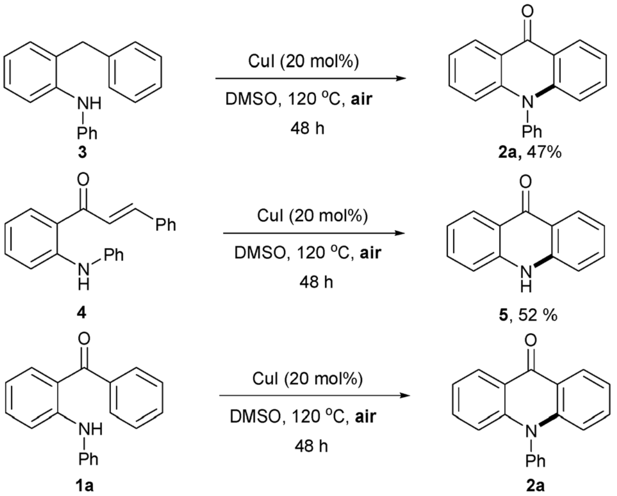
[a] Reaction conditions: **1** (0.3 mmol), CuI (20 mol%) in DMSO (1.6 mL) were stirred at 120 °C under air (1 atm) for 48 h. [b] Isolated yield.

With the optimized reaction conditions in hand, the scope of this direct amination was explored (Table 2). Several functional groups, such as methyl (entries 2–4), phenyl (entry 5), chloro (entry 8), fluoro (entry 9), ethoxycarbonyl (entry 10), cyano (entry 11) and trifluoromethyl (entry 12), on the *N*-aryl moiety were well-tolerated, delivering the corresponding products in moderate to good yields. In general, electron-rich substrates were more reactive than electron-deficient ones in terms of yields. To our delight, iodo and bromo substituents were also found to be compatible with the reaction, affording the acridones which could be readily subjected to further transformation (entries 6 and 7). Substrates **1m–1t** worked well to provide the corresponding acridones in 30–85% yields (entries 13–20).

It is worth noting that *N*-(2-benzylphenyl)benzenamine **3** was completely consumed and successfully converted to *N*-phenyl acridone **2a** in 47% yield under the optimized conditions (Scheme 2). Interestingly, chalcone **4** was aminated to give 10*H*-acridin-9-one **5** under the same conditions. We could detect 10-phenyl-9,10-dihydroacridine by GC-MS analysis during the reaction, so the ketone group may not be necessary for the reactivity.

Three separate reactions were conducted by stoichiometric addition of an electron-transfer scavenger (1,4-dinitrobenzene), a radical clock (diallyl ether) or a radical inhibitor (hydroquinone).[8] The reaction still proceeded smoothly to afford the desired product (Scheme 2). These observed results suggest that the radical process is not involved in this transformation.

On the basis of these preliminary results, a catalytic cycle of this transformation was hypothesized as shown in Fig. 1. Initially, a reactive Cu(III) intermediate **A** is formed by the reaction of Cu(I) and substrate **1** with the aid of O_2 *in situ*[6] *via* an electrophilic metallation or a C–H bond activation.[5b,9,10] Reductive elimination delivers the product **2** with concurrent formation of Cu(I).



------	78%
1,4-Dinitrobenzene (1.0 equiv)	69%
Diallyl ether (1.0 equiv)	74%
Hydroquinone (1.0 equiv)	48%

Scheme 2 Mechanism probing experiments.

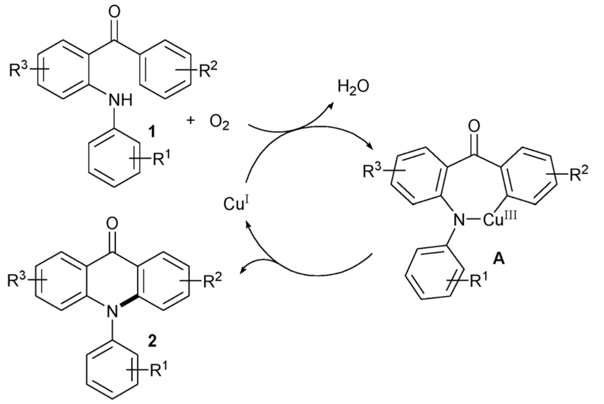


Fig. 1 A possible catalytic cycle for C–H bond amination.

In conclusion, we have demonstrated a copper-catalyzed approach for the synthesis of *N*-aryl acridones *via* sp^2 C–H bond amination using air as oxidant under neutral conditions. This reaction not only provides a complementary method for constructing medicinally important acridones, but also offers a new strategy for sp^2 C–H bond amination. Further studies on the reaction scope and the detailed mechanism are under investigation in our group.

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10 Control experiments showed that CuI and $Cu(OAc)_2$ could catalyze the transformation under air, but, under N_2, almost no product was detected (see Table S2 in ESI† for details). These results suggest that Cu(III) species may be involved in this transformation.